



# Non-anastomotic strictures after transplanting a liver graft with an accidentally ligated and unflushed common bile duct: A case report

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## ABSTRACT

**INTRODUCTION:** Non-anastomotic biliary strictures (NAS) represent a major cause of morbidity, graft loss, and mortality after liver transplantation (LTx). NAS can result from an ischemic/immune-mediated injury, or from the cytotoxic effect that bile salts have on the biliary mucosa under hypothermic conditions. For this reason it is crucial to flush the bile duct at the time of procurement.

**PRESENTATION OF CASE:** We report a case of an imported liver with an accidentally ligated and subsequently completely unflushed common bile duct. The recipient was a 60 year-old man suffering from hepatocellular carcinoma and post-alcoholic cirrhosis. Post-operative course was uneventful and the patient was discharged after 18 days. Within 2 months post-transplantation, a rapidly evolving cholestasis was diagnosed. Endoscopic-retrograde-cholangio-pancreatography revealed diffuse NAS. Due to the rapid clinical and biochemical deterioration there was no other option than re-transplantation.

**DISCUSSION:** Suboptimally flushed bile ducts are often encountered and represent a risk factor for NAS after LTx. This unique case represented an extreme form where the biliary tree was not flushed at all. The dilemma of this unforeseen situation raised the question to transplant or discard this liver for transplantation? Given the organ shortage, the pressure to use less-than-ideal organs, the otherwise normal aspect of the liver and our incapacity to predict with certainty the development (or not) of NAS, we accepted this liver for transplantation.

**CONCLUSION:** This case illustrates *a contrario* the importance of flushing the bile duct and risk of extensive dissection of the hepatic hilum at the time of procurement.

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## 1. Introduction

NAS, also referred to as ischemic-type biliary strictures, ischemic cholangiopathy, or intra-hepatic biliary strictures remain the Achilles' heel of LTx. As NAS are usually resistant to any radiological and/or endoscopic intervention, they represent thus an important cause of morbidity, graft loss, additional costs, and mortality [1]. In addition to ischemic and immunological insults, surgical factors and direct cytotoxicity of bile salts on the epithelium of bile ducts may play a role in the development or prevention of NAS [1]. Scarce evidence based data and no validated consensus to protect the bile ducts during procurement/preservation/LTx are described. Here, we report the rapid development of diffuse NAS

after transplantation in our academic center of a liver graft whose bile duct had been accidentally ligated during procurement surgery, keeping the entire biliary tree exposed to stagnating cold bile during the cold preservation period. This work has been reported in line with the SCARE and PROCESS criteria [2,3].

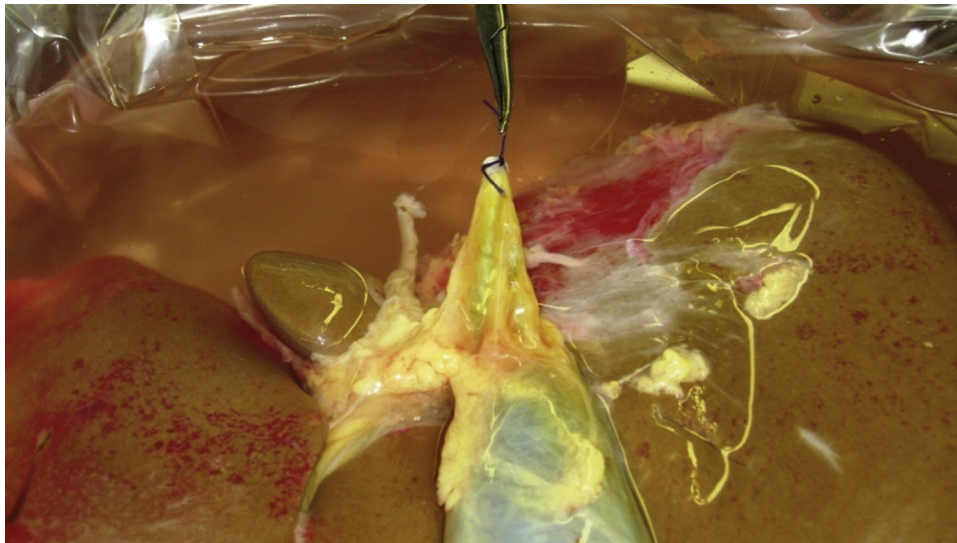
## 2. Patient presentation

A 60-year-old Caucasian 83 kg male (blood group A+, CMV negative) had been listed for LTx because of hepatocellular carcinoma and post-alcoholic cirrhosis. He was offered a liver graft from a 68-year-old, 90 kg (blood group A+, CMV negative) male donor who had succumbed due to an intra-cerebral bleeding. The donor was hemodynamically stable and liver function tests were normal. The liver was flushed-out with 6000 mL of Histidine-Tryptophan-Ketoglutarate solution. Normal anatomy and macroscopic appearance (including absence of steatosis) were reported by the procurement team. At arrival of the liver at our academic center, we found that the common bile duct had been accidentally ligated during the procurement and had not been

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**Fig. 1.** Liver graft with an accidentally ligated common bile duct, leaving the biliary tree and the gallbladder completely unflushed during the cold preservation.

flushed at all. In addition, the gallbladder was not opened nor flushed (Fig. 1), leaving the graft with stagnating bile for at least 4 h 38 min. The ligated common bile duct was then opened and the cold bile flushed-out abundantly. The transplantation was straightforward; total surgery time was 3 h and 30 min. Both cold and intra-operative warm ischemic times were kept short: 8 h 4 min and 49 min, respectively. Biliary reconstruction was achieved by an end-to-end duct-to-duct anastomosis without T-tube. Hereby, the donor common bile duct was appropriately shortened and appeared well-vascularized. The immediate postoperative course was uneventful. The peak of aspartate amino-transferase (AST) and alanine amino-transferase (ALT), defined as the highest value within the first 3 days post-transplantation, was 234 IU/L and 154 IU/L, respectively. AST/ALT then slightly decreased until a normal range at discharge. Alkaline phosphatases decreased during the first postoperative days and started increase around day 10 to reach a level of 3 times higher than the superior limit of normality at discharge. The recipient was discharged 18 days post-transplantation with satisfactory liver function. However, during the out-patient follow-up, the cholestasis continued to evolve (clinical jaundice, pruritis, no fever and total bilirubin >12 mg/dl, levels of Alkaline phosphatase 10 times higher than the normal range). Endoscopic-retrograde-cholangio-pancreaticography revealed filiform intra-hepatic biliary ducts with multiple narrowings (“dead tree” image) typical of NAS (Fig. 2) and the aspect of a local ischemia at the site of the biliary anastomosis. The potential anastomotic stenosis was dilated without any relief of symptoms. Hepatic artery occlusion or stenosis were excluded by repeated echo doppler examinations and CT scan (Fig. 3). Acute or accelerated chronic rejection (vanishing bile duct syndrome) were excluded on histology. Due to the rapid clinical and biochemical deterioration and the absence of alternative therapeutic options, the patient had to be listed for re-transplantation 10 weeks after the first transplantation (Clavien-Dindo grade IIIb complication). He was successfully re-transplanted 117 days after the first transplantation. The hepatic artery was found widely patent. Microscopic analysis of the explanted liver confirmed the extensive scarring and necrosis of the bile ducts and early onset of biliary cirrhosis (Fig. 4).

### 3. Discussion

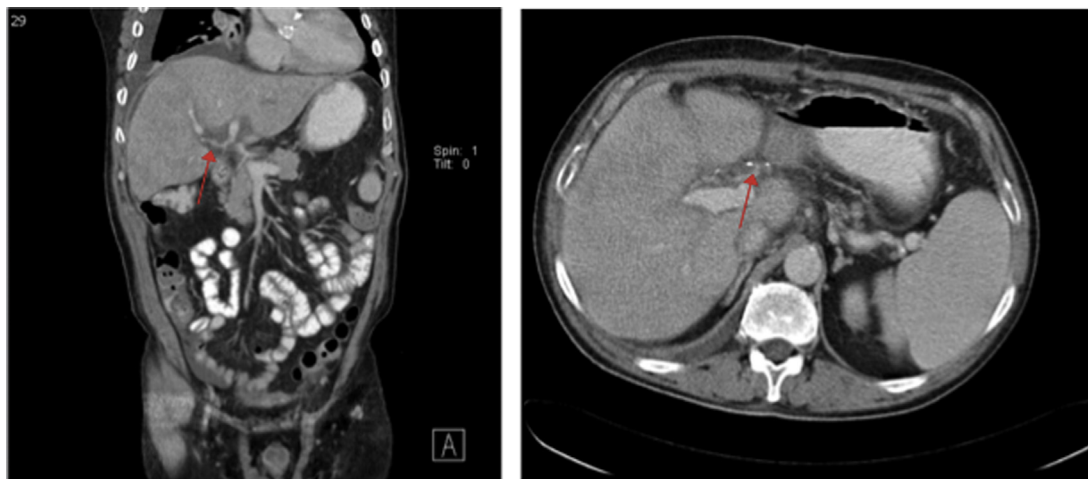
The incidence of NAS in LTx varies between 1 and 20% [1] for grafts originating from death donors and can be as high as 34%



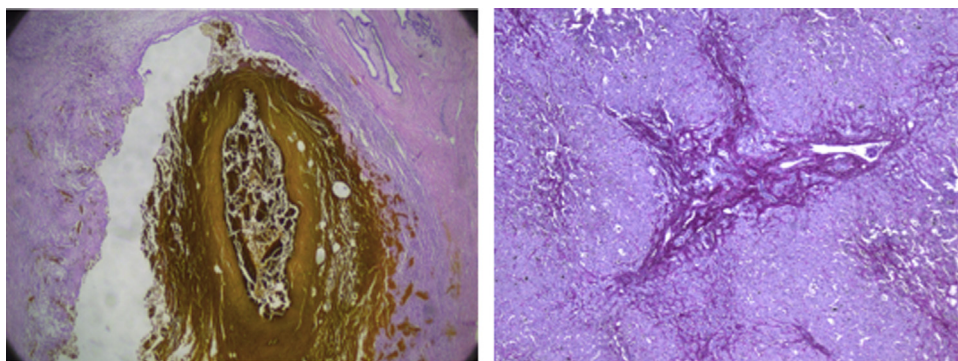
**Fig. 2.** Endoscopic-retrograde-cholangio-pancreaticography at 2 months post liver transplantation reveals mainly diffuse filiform intra-hepatic biliary ducts with multiple narrowings (“dead tree” image) typical of NAS and the aspect of a local ischemia at the site of the biliary anastomosis.

for grafts originating from donation after circulatory death donors [4]. NAS are associated with higher resource utilization, increased recipient morbidity and mortality and a higher incidence of retransplantation [1]. In contrast with localized biliary strictures that can be treated endoscopically or surgically, the therapeutic options for diffuse intra-hepatic NAS are virtually inexistent and retransplantation is often the only option [5].

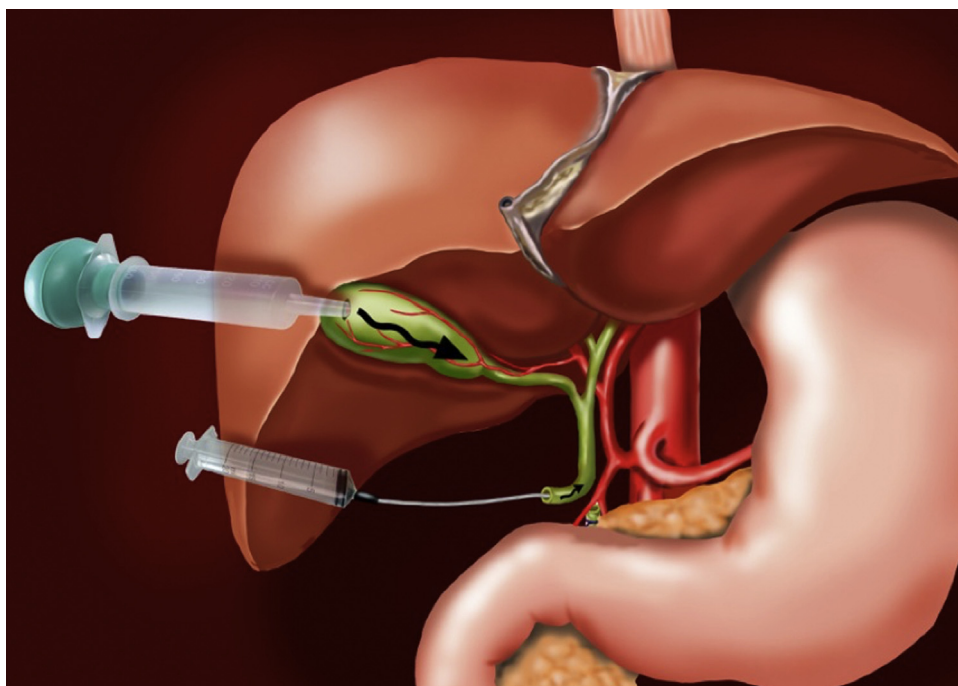
Although the detailed operating mechanisms remain unclear, NAS seem to be caused by an injury to the cholangiocytes and the biliary mucosa. Proposed mechanisms underlying the pathogenesis of NAS are related to ischemia and ischemia-reperfusion injury, immune mediated injury, or by direct cytotoxic effect of hydrophobic bile salts on the biliary mucosa under hypothermic conditions [1]. Interestingly, early after reperfusion bile composition alters resulting in a more toxic bile due to an imbalance between excreted biliary salts and phospholipids [6–8]. Risk factors for NAS include grafts from donation after circulatory death donors [4,9], highly viscous preservation solutions [10], prolonged cold ischemia time [1], severe ischemia-reperfusion injury [11], hepatic artery thrombo-



**Fig. 3.** CT with IV contrast, one month after transplantation, showing a patent hepatic artery.



**Fig. 4.** Microscopic section of the explanted transplant liver showing extensive scarring and necrosis of the bile ducts (left) and early onset of biliary cirrhosis (right, Sirius red staining).



**Fig. 5.** Abundant and repeated flushing of both the common bile duct and the gallbladder in- and ex- situ during the procurement.



sis and stenosis [12], ABO incompatibility [13], CMV infection [14], liver diseases with an immune component [15] and last but not least, an inadequate flush out of bile before the cold ischemia [1].

It is generally recognized that stagnation of cold bile and hydrophobic bile salts are deleterious for cholangiocytes and hepatocytes due to their detergent effects towards lipid cellular membranes [1]. Studies in rabbits and in rats have shown that cold preservation induces extensive biliary autolysis [16,17]. This damage is directly related to the presence of bile in the biliary tract and can be reduced by elimination of stagnating bile prior to cold preservation as confirmed later in man [18]. In the case described here, the short time-span between the transplantation and the development of biliary strictures and the absence of other known risk factors for biliary complications strongly support the causal link between the stagnation of cold bile and the development of NAS.

Given the organ shortage, there is increasing pressure to use less-than-ideal organs. We were confronted with the dilemma of transplanting this liver and exposing the recipient to a higher risk of biliary strictures or discarding it and potentially losing the chance of a life-saving transplant. Given the otherwise normal macroscopic appearance of this liver, our incapacity to predict the development of non-anastomotic biliary strictures with certainty, we decided to transplant this liver.

This case obviously represents an extreme form of damage to the biliary tree by stagnating cold bile. However, suboptimal washout and persisting bile in the biliary tree is – unfortunately – not a rare event. While there is general acceptance that flushing the bile duct is an essential part of a standard procurement before the cold preservation [19,20], there are no internationally accepted guidelines on the best modality to achieve that: timing of flushing; single or repeated flushing; type, temperature, pressure and volume of the flushing solution? It seems reasonable to recommend abundant and repeated flushing of both the common bile duct and the gallbladder (Fig. 5) *in situ* during the procurement and to repeat this flushing *ex situ* on the back table until the biliary effluent is completely clear. Biliary flushing should be done gently at low pressure to avoid mechanical trauma to the biliary mucosa. In addition, it seems reasonable to recommend additional *ex situ* flushing of the portal vein and the hepatic artery with the preservation solution to ensure complete washout of the liver parenchyma and in particular the peri-biliary vascular plexus, thereby optimizing the preservation of the bile ducts. A cholecystectomy and/or the ligation of the cystic duct are sometimes performed to avoid further contamination of stagnating bile during the cold storage. Although there is a lack of scientific evidence regarding optimal management of the gallbladder, one must be aware that any manoeuvres and dissection made to the hepatoduodenal ligament, done sometimes expediently, by less-experienced surgeons and under suboptimal operative conditions, can lead to accidental damage in the liver hilum or –as probably occurred in this case– accidental ligation of the main bile duct.

#### 4. Conclusion

In conclusion, this case tragically illustrates for the first time the cytotoxic effect that stagnating cold bile caused by the ligation of the common bile duct during the procurement has on the biliary mucosa and on the rapid subsequent onset of NAS in clinic. Based on this case, we believe that transplant surgeons confronted with an accidentally ligated and completely unflushed common bile duct should be reluctant to transplant such livers. The importance of preserving the bile duct cannot be stressed enough. Take home messages can be expressed as follow: first, abundantly flushing the bile duct during and immediately after procurement and

prior to cold storage. Secondly, surgeons should avoid any iatrogenic damage of the hepatic hilum due to extensive dissection. Finally, guidelines on bile duct protection widely accepted by the LTx community are urgently needed.

#### Conflicts of interest

No conflicts to disclose.

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JP holds an IGL named chair from the IGL-group.

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#### Ethical approval

The study was approved by the Leuven University Hospital's Institutional Review Board (560453).

#### Consent

No consent was obtained from the patient who was sufficiently anonymised in this case report, not to cause harm to the patient nor his family.

#### Author contribution

Nicolas Meurisse wrote the paper.

Jacques Pirenne and Diethard Monbaliu critically reread the manuscript and approved the final version.

#### Guarantor

D. Monbaliu, N. Meurisse and J. Pirenne.

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